

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Methamphetamine and cannabis abuse in adolescence: a quasi-experimental study on specific and long-term neurocognitive effects
<b>AUTHORS</b>	Cuzen, Natalie; Koopowitz, Sheri-Michelle; Ferrett, Helen; Stein, Dan; Yurgelun-Todd, Deborah

### VERSION 1 - REVIEW

<b>REVIEWER</b>	UW Preuss Martin-Luther University Halle-Wittenberg, Prignitz County Hospital, Germany
<b>REVIEW RETURNED</b>	13-Jul-2014

<b>GENERAL COMMENTS</b>	<p>The manuscript reports results from a neuropsychological assessment study on cannabis and/or methamphetamine use disordered subjects vs. controls. Individuals aged 13 to 18 with either cannabis/methamphetamine use alone or combined were recruited and underwent a battery of neurocognitive testing at baseline and at 12 month follow-up. Results indicate that the combined group had widespread cognitive deficits at baseline, the methamphetamine only group showed impairments in self-monitoring abilities at baseline and follow-up. The authors conclude that a combined use of both substances results in significant and long-enduring cognitive deficits compared to methamphetamine use only.</p> <p>The papers deals with the relevant issue of cognitive deficits in cannabis- and/or methamphetamine users in a prospective study design. The strengths of the paper include the use of well-evaluated instruments and carefully selected sample.</p> <p>Some issues should be considered to further improve the paper:</p> <p>Major issues:</p> <ol style="list-style-type: none"> <li>1. Introduction: the authors did not mention in their introductory section what neurocognitive deficits are already reported in the literature. This impairs their rationale not only for the study in general but also for the neuropsychological tests they chose for assessment of the subjects. There are several recent reviews on cognitive deficits in either cannabis or methamphetamine users (e.g. Lisdahl et al <i>Front Psychiatry</i>. 2013; Crane et al <i>Neuropsychol Rev</i>. 2013; Dean et al <i>Neuropsychopharmacology</i>. 2013) which should be mentioned.</li> <li>2. Following that, the number of subjects is rather small while the re-interview-rate is high. To counter the low number of subjects (which makes the sample and the results "vulnerable" to outliers in neuropsychological testing) the authors should provide a</li> </ol>
-------------------------	--

	<p>power/sample size analysis (based on previous studies) to prove that the sample size is sufficient to test for all potential cognitive impairments the authors chose to employ.</p> <p>Minor issues</p> <ol style="list-style-type: none"> <li>1. The authors should mention the low sample size as a limitation. The focus on adolescents aged 14 to 18 is more of a strength than a limitation to the study.</li> <li>2. While the authors mention in their statistics section that they employed ANOVA for analysis of sociodemographic and other variables, they do not mention the test statistics (F-value, DF, and level of significance, specific group differences at baseline or follow-up testing) in the tables. Further, based on the small number of subjects and potential multiple testing (e.g. table 5), did the authors consider Bonferroni or other correction of p? I suggest the authors reduce the number of tests employed and justify the use.</li> </ol>
--	---

<b>REVIEWER</b>	Reuben Robbins New York State Psychiatric Institute and Columbia University
<b>REVIEW RETURNED</b>	28-Jul-2014

<b>GENERAL COMMENTS</b>	<p>This is an interesting and well-written manuscript that set out to examine the neuropsychological effects of methamphetamine abuse. The study had 3 groups - methamphetamine abusers only, methamphetamine and cannabis abusers, and non-substance using controls. The methods and results are clearly written.</p> <p>There are a few points that detract from the paper and its conclusions. First, it is not clear why certain measures were included in this study. While the study set out to examine neuropsychological effects of methamphetamine abuse, the Methods indicate that participants were also administered measures of disinhibitory personality traits. There are also repeated neuropsychological measures for two of the three groups.</p> <p>The introduction is brief and seems to indicate that the focus of the paper is on neurocognition, yet the study also measured various personality traits. There is very little background on the relationship to neurocognition and personality traits. The introduction states that, "Despite overall increased rates of methamphetamine abuse, several fundamental questions about the consequences of such abuse remain incompletely unanswered..." However, the authors do not give much background on the importance of understanding the importance of "differential consequences of methamphetamine abuse with or without cannabis use on adolescent brain function and structure..." No literature is cited. In addition, the authors state, "the long-term neurocognitive outcome ....with minimal externalizing psychopathology remains an open question." What, exactly, is the question? Is it what are the long term consequences of meth abuse on neurocognition and externalizing behavior? Or is it the long term effects of meth abuse among those abusers who exhibit little externalizing behavior? Whether it is one of these or another question, it will help the reader to understand the context within which the question is being asked and why answering the question is of importance to the field.</p> <p>The abstract does not address the issue of personality traits. The authors also do not make any hypotheses about differences in</p>
-------------------------	---

	<p>neuropsychological test performance or personality traits. While the authors have some important follow-up data on neurocognition for two of the groups, the paper gets a bit confusing as it sets out to compare meth only to meth and cannabis abusers.</p> <p>The study is interesting and can add to the literature on adolescent methamphetamine abuse and neurocognition. However, the paper needs 1) clarification about what exactly the study is looking at/trying to answer, 2) some elaboration on what is known or not known about these groups, and what, if there are any, hypotheses the authors have about their findings, and 3) more background about personality traits, brain structures/functions, and neurocognition.</p>
--	--

### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1

The reviewer indicated that a number of neurocognitive effects of methamphetamine have already been mentioned in the literature, but not in the paper. We have now included these references.

As suggested by the reviewer, we now discuss the relatively small sample size in more detail, and highlight this as a limitation. We understand that the small sample size is a limitation and not sufficiently powered, but the results are still valuable.

Furthermore, we pay more attention to justifying the use of tests in the results section, and we reduce the number of tests, as suggested by the reviewer.

This reviewer noted that the strengths of this paper include using well-evaluated measures and a carefully selected sample.

It was also mentioned that although the sample size was a limitation, using adolescents is a strength for the study.

This reviewer suggested that a Bonferroni correction be done. However, in this preliminary study, we elected not to do the Bonferroni correction for multiple comparisons.

#### Reviewer 2

This reviewer felt that the methods and results sections were clearly written. He also felt that it was unclear why personality measures were used. We have decided to remove this from the manuscript, as it did detract from the main findings of the research.

As suggested by the reviewer, we now provide more information about the different groups, and elaborate the hypotheses used.

This reviewer suggested that we provide more background about the relevant brain structures in the discussion, which we have now done.

Furthermore, it was noted by this reviewer that only two of the three groups were followed up, and we emphasize this as a limitation in the discussion section.

Once again, we thank the reviewers for the time taken to give us feedback. We believe that the manuscript has been strengthened as a result of these changes, and we hope that is now suitable for publication.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Ulrich W Preuss KKH Prignitz, MLU Halle-Wittenberg, Germany
<b>REVIEW RETURNED</b>	11-Oct-2014

<b>GENERAL COMMENTS</b>	Authors have responded to the reviewer's comments appropriately.
-------------------------	--